THE AMERICAN JOURNAL OF CLINICAL NUTRITION
Vol. 23, No. 6, June, 1970, pp. 843-847
*Printed in U.S.A.*

# Folate Deficiency Conditioned by Lactation[1]

J. METZ

THE MEGALOBLASTIC ANEMIAS associated with pregnancy are usually the result of folate deficiency. Osler (1) is accredited with the first description of the disease, and he noted that the common form occurred after delivery. Of 318 cases collected from the literature by Chanarin et al. (2), the diagnosis was made after delivery in over 50%. When megaloblastic anemia manifests itself shortly after delivery, pregnancy alone probably has been sufficient to precipitate critical folate deficiency, and the term, megaloblastic anemia of pregnancy or of the puerperium, is applicable. In recent years, attention has been drawn to a form of folate deficiency presenting many months, even longer than 1 year, after delivery (3, 4), and in some population groups as many as 20% of the patients with "megaloblastic anemia of pregnancy" may present at intervals of longer than 6 months after delivery (5). In these patients, the long interval after delivery makes it unlikely that the disease is directly related to events in pregnancy. In one such group, it was noted that the patients were lactating, and the term "megaloblastic anemia associated with lactation" probably is more suitable.

There is considerable evidence that this megaloblastic anemia occurring in lactating patients is associated with folate deficiency. Serum folate levels are low (6), injected folic acid is cleared abnormally rapidly from the plasma (7), and increased formiminoglutamic acid (FIGLU) excretion follows histidine loading (8). Hematologic remission can be induced with small doses of folic acid (9), but not with physiological doses of vitamin $B_{12}$. The serum vitamin $B_{12}$ levels are usually within normal limits (10). That the folate deficiency might be related etiologically to lactation was an obvious possibility. Megaloblastic anemia occurring many months after delivery was found particularly in populations subsisting on suboptimal diets with deficient dietary folate intake (3, 4). However, even in malnourished populations deficient folate intake does not usually result in overt megaloblastic anemia in adults unless conditioned by pregnancy, malabsorption, increased hemolysis, or infection. None of these conditioning factors was consistently present, although prolonged lactation was invariable (5).

## EVIDENCE THAT LACTATION IS A CONDITIONING FACTOR FOR FOLATE DEFICIENCY

Evidence from a number of sources suggests that lactation may drain maternal folate stores. Folate nutrition tests on large groups of pregnant patients reveal an increasing incidence of deficiency as pregnancy progresses (11–14). In patients with a high incidence of malnutrition, the serum folate level at term may average only 50% that of nonpregnant subjects (14). Following delivery, maternal folate nutrition improves as witnessed by a rise in the serum folate concentration (14). This improvement is short-lived in populations whose dietary folate intake is suboptimal, for folate nutrition again tends to

[1] From the Department of Haematology, South African Institute for Medical Research, Johannesburg, South Africa.

deteriorate as lactation progresses. After 12 weeks lactation, 38% of the subjects showed serum folate levels of less than 2.5 μg/ml (15). Formiminoglutamic acid excretion increased after 8 weeks of lactation and continued to rise as the duration of lactation increased; after 12 weeks of lactation, 49% of subjects excreted excessive quantities of FIGLU after histidine loading. This deterioration in folate nutrition was prevented by supplementation with folic acid during lactation (15).

Further evidence that lactation may drain maternal folate stores comes from studies of maternal requirements for folate during lactation. The smallest dose of folic acid that will produce hematologic response in patients with folate-deficient megaloblastic anemia is higher in lactating subjects. In nonlactating patients who do not have an increased folate requirement, a daily dose of 100 μg of folic acid is adequate to induce hematologic response (16). A daily dose of folic acid as high as 400 μg is required to produce significant reticulocytosis for lactating patients, and even then a secondary reticulocyte peak often can be induced with larger doses (9). Daily doses in the order of 200 μg fail to produce a hematologic response (9).

Experiments aimed at determining the minimal requirement for folate have revealed increased maternal requirements during lactation (17). In healthy, nonlactating, adult females the minimal daily folate requirement is about 50 μg/day (18). The smallest amount of folic acid required to maintain the serum folate level of a lactating female fed an experimental low folate diet is in the order of 200–300 μg/day (17).

The supply of folate to the infant via breast milk takes precedence over maternal folate needs. Thus, when lactating subjects are fed an experimental low folate diet the maternal serum folate level falls rapidly, whereas the breast milk folate remains constant (17). If the diet is continued, the breast milk folate starts to fall some 10 days after the serum folate level begins to decrease. In these lactating subjects receiving a low folate diet, the administration of small doses of folic acid (less than the minimal daily requirement) results in a rapid increase in the milk folate, but the serum folate concentration fails to rise. Studies of lactating patients with folate-deficient megaloblastic anemia reveal a similar pattern. Daily administration of 100-μg doses of folic acid results in an appreciable rise in milk folate concentration, but the serum folate and reticulocyte count remain unchanged (19). If the daily dose is increased to 200 μg, the breast milk folate rises rapidly, whereas reticulocytosis is delayed to the 10th day, and the serum folate level fails to rise in spite of persistently elevated milk folate concentrations. Thus, even with folate deficiency severe enough to result in megaloblastic anemia in the mother, orally administered folic acid is taken up by breast milk in preference to the hemopoietic system. Studies on the binding of folic acid by breast milk compared with serum suggest a physiologic mechanism whereby folate is preferentially concentrated in the milk. Binding of folic acid by serum is weaker than in milk; there is a firm binder for folic acid in milk that is not present in serum (19). Yet further evidence of the preferential deviation of folate into the breast-fed infant comes from studies during prolonged lactation in women subsisting on suboptimal diets (15). The incidence of anemia in lactating females is lower if folic acid supplementation is administered to the mother. However, there is no difference in the hematocrit or weight of infants breast fed by mothers receiving folic acid supplementation compared with mothers whose diet is not supplemented.

There are data from rat experiments indicating that lactation alone can produce maternal folate deficiency. In the late 1940's it was noted that folic acid defi-

ciency was difficult to induce in the rat by dietary deprivation only, unless intestinal synthesis was inhibited by the inclusion of sulfonamide in the diet. However, in the absence of a sulfonamide (20), the stress of lactation resulted in deficiency in as short a time as 3 weeks. The leukopenia and granulocytopenia produced under these conditions were especially severe. High levels of folic acid were necessary for the prevention of folate deficiency in the lactating rat; the amount of folic acid required to maintain maternal body weight and circulating leukocytes was 8 times that required by the nonlactating rat. Nelson and Evans (21) subsequently reported that the effects of folate deficiency in the lactating rat improved when lactation ended, despite the continued presence of sulfonamide in the diet. Williamson (22) noted that in the rat the maternal requirement for folic acid appeared to be very much greater during lactation than during pregnancy.

From all this data there can be little doubt that lactation may be a conditioning factor for folate deficiency.

### NUTRITIONAL SIGNIFICANCE OF THE INCREASED FOLATE REQUIREMENT DURING LACTATION

With the widespread use of artificial foods for infants, prolonged lactation is a rarity in developed populations. It is not surprising, therefore, that when nutritional folate deficiency occurs in the adult female in these populations it usually presents during pregnancy or the immediate postpartum period. In developed populations, even with prolonged lactation, critical folate deficiency is unlikely, for the folate content of their diets is usually adequate to cover the increased requirement during lactation (23, 24). Furthermore, the practice of routine supplementation with folic acid during pregnancy, often with an amount of folic acid well in excess of maternal requirements during pregnancy, provides the nursing mother with adequate folate stores for even prolonged lactation.

In developing populations, however, the position is often quite different. Dietary folate intake is usually suboptimal, and prolonged lactation is not unusual. The irregular attendance of expectant mothers at prenatal clinics results in their receiving little or no folic acid supplementation during pregnancy, the added folate requirements of which produce a negative folate balance. Depending on the degree of dietary folate deficiency and the size of the maternal folate stores, megaloblastic anemia may develop toward the end of pregnancy. If deficiency is not severe enough to result in megaloblastic anemia during pregnancy, these patients nonetheless enter lactation with diminished folate stores. The added folate requirement during lactation in a subject whose folate intake is low and whose folate stores have been depleted by pregnancy may then result in severe megaloblastic anemia. Therefore, in some developing populations in Africa and Asia, the commonest form of megaloblastic anemia in adults is that which follows pregnancy (3, 4). Of 56 Burmese women with folate-deficient megaloblastic anemia, 5 were pregnant, while the remainder presented 2–18 months after delivery (4). These subjects lacked fresh vegetables and fruits in their diet and there seemed little doubt that the food consumed by them was extremely poor in folates.

If studies were carried out on other population groups in whom dietary folate is suboptimal and prolonged lactation the rule, it is likely that a high incidence of folate deficiency during lactation would be revealed. In terms of number of subjects affected, lactation may be a conditioning factor of major importance in the worldwide incidence of folate deficiency. Furthermore, lactating subjects may be the ideal group to sample for information on the prevalence of folate deficiency, for the reservations held on the interpretation of

tests of folate nutrition in pregnant subjects (25) and malnourished infants (26) do not apply to this group.

The recognition of the widespread occurrence of folate deficiency during pregnancy has led to the acceptance of supplementation with folic acid as routine in many prenatal clinics. With such supplementation, megaloblastic anemia associated with pregnancy can be eliminated (27). In the South African Bantu, daily supplementation with 5 mg folic acid during pregnancy will reduce the incidence of megaloblastic anemia during pregnancy and the puerperium, as well as the form associated with prolonged lactation, (T. Edelstein and J. Metz, unpublished data). With folic acid supplementation of this order during pregnancy, continued supplementation during lactation is unnecessary. A daily dose of 5 mg folic acid during pregnancy is, however, far in excess of the 100–300 $\mu$g recommended for routine supplementation to subjects subsisting on a normal diet (28–30). It is unlikely that in populations with low dietary folate a daily supplement of 100–300 $\mu$g folic acid given during pregnancy would be adequate to cover the requirements of prolonged lactation also. Thus, in these populations, supplementation should be continued during lactation. A more practical approach may be to supplement during pregnancy only but with a larger daily dose of folic acid. This larger dose may, however, be harmful to patients with pernicious anemia that, although rare in this age group, has been reported in young Bantu females (31).

## SUMMARY

Folate-deficient megaloblastic anemia occurs in lactating subjects many months after delivery of their infants. Lactation produces a drain on maternal folate stores as evidenced by *1*) the increasing incidence of abnormality in tests of folate nutrition as lactation progresses, *2*) the increased amounts of folic acid required to induce hematological response in lactating patients with megaloblastic anemia, *3*) the increased minimal daily requirement for folate by lactating subjects, and *4*) the relative ease with which lactation produces folate deficiency in the rat. The supply of folate to the breast milk takes precedence over maternal needs even when the mother is severely folate deficient. The increased folate requirement during lactation may be of considerable importance in the nutrition of developing populations where dietary folate intake is suboptimal and prolonged lactation the rule. In these populations lactation may be a common conditioning factor for severe folate deficiency in adults.

I wish to thank the Director of the South African Institute for Medical Research for facilities to carry out some of the studies cited in this paper.

## REFERENCES

1. Osler, W. Observations on the severe anaemias of pregnancy and the post-partum state. *Brit. Med. J.* 1: 1, 1919.
2. Chanarin, I., B. M. MacGibbon, W. J. O'Sullivan and D. L. Mollin. Folic acid deficiency in pregnancy. The pathogenesis of megaloblastic anaemia of pregnancy. *Lancet* 11: 634, 1959.
3. Cassel, R., and J. Metz. On the incidence of some blood disorders in the South African Bantu. *Med. Proc.* 4: 278, 1958.
4. Izak, G., M. Rachmilewitz, S. Zan and N. Grossowicz. The effect of small doses of folic acid in nutritional megaloblastic anemia. *Am. J. Clin. Nutr.* 13: 369, 1963.
5. Metz, J. Megaloblastic anaemia in a malnourished population. *Proc. 7th. Intern. Congr. Intern. Soc. Hematol., Rome.* New York: Grune & Stratton, 1958, vol. 2, p. 339.
6. Stevens, K., J. Metz, V. Brandt and L. van Broekhuizen. Serum vitamin $B_{12}$, folic acid and urinary formiminoglutamic acid in megaloblastic anaemias in South African Bantu adults. *E. African Med. J.* 39: 222, 1962.
7. Metz, J., K. Stevens, S. Krawitz and V. Brandt. The plasma clearance of injected doses of folic acid as an index of folic acid deficiency. *J. Clin. Pathol.* 14: 622, 1961.
8. Metz, J., K. Stevens and V. Brandt. Urinary formiminoglutamic acid in the megaloblastic anaemias associated with pregnancy and malnutrition. *Brit. Med. J.* 1: 1440, 1962.

9. Stevens, K., and J. Metz. The absorption of folic acid in megaloblastic anaemia associated with pregnancy. *Trans. Roy. Soc. Trop. Med. Hyg.* 58: 510, 1964.
10. Metz, J., V. Brandt and K. Stevens. Vitamin $B_{12}$ and megaloblastic anaemia in South African Bantu. *Brit. Med. J.* 1: 24, 1962.
11. Solomons, E., S. L. Lee, M. Wasserman and J. Malkin. Association of anaemia in pregnancy and folic acid deficiency. *J. Obstet. Gynaecol. Brit. Commonwealth* 69: 724, 1962.
12. Hansen, A. H., and H. V. Klewesahl-Palm. Blood folic acid levels and clearance rate of injected folic acid in normal pregnancy and puerperium. *Scand. J. Clin. Lab. Invest.* 15: Suppl. 69, 78, 1963.
13. Ball, E. W., and C. Giles. Folic acid and vitamin $B_{12}$ levels in pregnancy and their relation to megaloblastic anemia. *J. Clin. Pathol.* 17: 165, 1964.
14. Edelstein, T., K. Stevens, V. Brandt, N. Baumslag and J. Metz. Tests of folate and vitamin $B_{12}$ nutrition during pregnancy and the puerperium in a population subsisting on a suboptimal diet. *J. Obstet. Gynaecol. Brit. Commonwealth* 73: 197, 1966.
15. Shapiro, J., H. W. Alberts, P. Welch and J. Metz. Folate and vitamin $B_{12}$ deficiency associated with lactation. *Brit. J. Haematol.* 11: 498, 1965.
16. Herbert, V. Current concepts in therapy: megaloblastic anemia. *New Engl. J. Med.* 268: 201, 368, 1963.
17. Metz, J., and P. Hackland. Folate metabolism during lactation. *Congr. S. African Soc. Haematol. Cape Town,* July 1968.
18. Herbert, V. Minimal daily adult folate requirement. *Arch. Internal Med.* 110: 649, 1962.
19. Metz, J., R. Zalusky and V. Herbert. Folic acid binding by serum and milk. *Am. J. Clin. Nutr.* 21: 289, 1968.
20. Nelson, M. M., and H. M. Evans. The beneficial effects of synthetic pteroylglutamine acid on lactation. *Arch. Biochem.* 13: 265, 1947.
21. Nelson, M. M., and H. M. Evans. The effect of succinylsulphathiazole on pteroylglutamine deficiency during lactation in the rat. *Arch. Biochem.* 18: 153, 1948.
22. Williamson, M. B. Increased requirement for pteroylglutamic acid during lactation. *Proc. Soc. Exptl. Biol. Med.* 70: 336, 1949.
23. Butterworth, C. E., R. Santine and W. B. Frommeyer. The pteroylglutamate components of American diets as determined by chromatographic fractionation. *J. Clin. Invest.* 42: 1929, 1963.
24. Chanarin, I., D. Rothman, J. Perry and D. Stratfull. Normal dietary folate, iron and protein intake, with particular reference to pregnancy. *Brit. Med. J.* 2: 394, 1968.
25. Chanarin, I., D. Rothman and E. J. Watson-Williams. Normal formiminoglutamic acid excretion in megaloblastic anaemia in pregnancy. Studies on histidine metabolism in pregnancy. *Lancet* 1: 1068, 1963.
26. Spector, I., H. C. Falcke, Y. Yoffe and J. Metz. Observations on urocanic acid and formiminoglutamic acid excretion in infants with protein malnutrition. *Am. J. Clin. Nutr.* 18: 426, 1966.
27. Lowenstein, L., C. Pick and N. W. Philpott. Megaloblastic anemia of pregnancy and the purperium. *Am. J. Obstet. Gynecol.* 70: 1309, 1955.
28. Alperin, J. B., H. T. Hutchinson and W. C. Levin. Studies of folic acid requirements in megaloblastic anemia of pregnancy. *Arch. Internal Med.* 117: 681, 1966.
29. Hansen, H., and G. Rybo. Folic acid dosage in profylactic treatment during pregnancy. *Acta Obstet. Gynecol. Scand.* 46: Suppl. 7, 107, 1967.
30. Chanarin, I., D. Rothman, A. Ward and J. Perry. Folate status and requirement in pregnancy. *Brit. Med. J.* 2: 390, 1968.
31. Metz, J., T. W. Randall and C. H. Kniep. Addisonian pernicious anaemia in young Bantu females. *Brit. Med. J.* 1: 178, 1961.